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Original Article

Ameliorative Effects of Curcumin on 5-Fluorouracil-Induced Liver and Kidney Toxicity in Rats

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ABSTRACT

5-Fluorouracil (5-FU) is a widely used chemotherapeutic drug associated with significant systemic toxicity, particularly affecting highly metabolic organs such as the liver and kidney. This toxicity limits its clinical efficacy. Curcumin, a natural polyphenol derived from turmeric (Curcuma longa), has demonstrated potent antioxidant, anti-inflammatory, and anti-apoptotic properties. This study investigates the protective effects of curcumin against 5-FU-induced hepatotoxicity, nephrotoxicity, and hematotoxicity in rats. 25 rats were subdivided into five groups of five animals each and treated for five weeks: the control group received tap water every day by gavage, while the second group received 5-FU (20 mg/kg BW twice a week) through an intraperitoneal injection. Groups 3, 4, and 5 followed the same treatment as the second group but also received daily doses of curcumin dissolved in corn oil (150, 300, and 450 mg/kg BW, respectively). At the end of the study, liver, kidney, and blood samples were collected to evaluate histopathological alterations and biochemical markers of liver and kidney functions, as well as blood cells. The results showed that administration of 5-FU caused a significant increase ($p < 0.05$) in serum levels of ALT, AST, ALP, BUN, and CRP, while it significantly reduced blood cells and hemoglobin. Co-administration of curcumin significantly ($p < 0.05$) reduced the effects of these alterations. Histopathological examination of liver and kidney tissues confirmed these findings, showing reduced vascular congestion, vacuolar degeneration, inflammatory cell infiltration, and cellular swelling. Curcumin supplementation, particularly in the CUR150+5-FU and CUR300+5-FU groups, greatly attenuated the 5-FU-induced biochemical and histopathological changes.

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1. Introduction

Cancer remains a major global health concern and a leading cause of mortality worldwide (de Porras et al., 2023). Chemotherapy is a common treatment for cancer patients. In addition, radiation therapy and surgical tumor removal may be choices. 5-Fluorouracil (5-FU) is a chemotherapeutic drug that disrupts nucleoside metabolism and attaches to RNA and DNA instead of uracil or thymine as a pyrimidine analogue, resulting in cytotoxicity and cellular apoptosis (Thomas and Zalcberg, 1998; Noordhuis et al., 2004; Zhang et al., 2008). 5-FU is widely used in the treatment of solid tumors such as colorectal cancers, head and neck cancers, and breast cancer (Goirand et al., 2018). While 5-FU demonstrated therapeutic efficacy, it also shows significant severe toxicity and adverse effects (Alvarez-Cabellos et al., 2007). Notable clinical adverse effects associated with 5-FU include

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hepatotoxicity and nephrotoxicity (Sengul et al., 2021; Ali, 2012).

Because of the vital role of the liver and kidney in the body, they are susceptible to many drug-induced toxicities. Multiple research studies indicate that 5-FU induces liver damage. Similar to other chemotherapy drugs, 5-FU stimulates the generation of reactive oxygen species (ROS) and prevents the antioxidant defense mechanisms (Behling et al., 2006). 5-FU affects the kidneys because it is catabolized in the liver to dihydrouracil, which is then cleaved into a-fluoro-b-alanine, ammonia, urea, and carbon dioxide (Rashid et al., 2014). Patients receiving 5-FU will also experience nephrotoxicity as a harmful toxic effect associated with the treatment (Rashid et al., 2014).

Recent studies focus on the application of natural compounds with antioxidant and anti-apoptotic properties to mitigate or eliminate different organ toxicities caused by chemotherapeutic drugs (Gelen Volkan, 2020). Curcumin (CUR) is a natural polyphenol compound and a major constituent derived from the rhizome of the Curcuma longa plant, known as turmeric (Aggarwal et al., 2003).

It's demonstrated that curcumin has different biological properties, such as antioxidant, antibacterial, antifungal, antiviral, anti-inflammatory, anticancer, and antiproliferative (Karthikeyan et al., 2020). Moreover, it has shown medicinal effects against many types of human illnesses, such as neurodegenerative diseases, arthritis, allergies, inflammatory bowel disease, kidney toxicity, liver toxicity, diabetes, multiple sclerosis, heart disease, and pulmonary fibrosis (Sharma et al., 2005; Menon and Sudheer, 2007; Karthikeyan et al., 2020).

“Curcumin as adjuvant therapy can enhance the therapeutical efficacy of different chemotherapeutic drugs, including cisplatin, 5-fluorouracil, vinca alkaloids, vinorelbine, and gemcitabine, while also mitigating their adverse effects through pharmacological interactions” (Crooker et al., 2018). Studies have indicated that the bioeffects of curcumin may be modulated by a series of target molecules, such as adhesion molecules, inflammatory factors, transcription and growth factors, apoptosis-related proteins, enzymes, and kinases (Fetoni et al., 2014).

In some conditions, phytochemical treatment is one of the most effective means to manage liver toxicity (Gedik et al., 2017). Curcumin's ability to protect the liver has been demonstrated in several studies on animal models of liver damage via many biological and pharmacological features, particularly by fighting oxidation, reducing inflammation, lowering blood lipid levels, and preventing fibrous formation (Khan et al., 2019). It also serves as a free radical scavenger, effectively neutralizing ROS and decreasing oxidative stress in liver cells (Khan et al., 2019). Similarly, curcumin has been demonstrated to have a kidney-protective effect in kidney injury associated with chronic renal failure, ischemia and reperfusion, diabetic nephropathy, and nephrotoxicity, which is caused by various toxic agents and chemotherapies (Sun et al., 2020).

This study aimed to investigate the protective effects of curcumin against liver, kidney, and hematotoxicity induced by 5-fluorouracil in rats, assessing its potential to mitigate 5-FU-induced hepatotoxicity, nephrotoxicity, and hematotoxicity by biochemical, hematological, and histopathological assessments.

2. Methodology

2.1 Chemicals

Curcumin (#8.20354, CAS-NO: 458-37-7) was obtained from Merck KGaA, Darmstadt, Germany. 5-fluorouracil (#F6627, CAS-NO:51-21-8) with purity ≥ 99% (HPLC) was acquired from Sigma-Aldrich Co., USA.

2.2 Animals

Twenty-five male Sprague Dawley rats (6–8 weeks old, weighing 165 ± 15 g) were acquired from an animal house at the University of Tikrit, Saladin, Iraq. All animals resided in plastic cages with

woodchip bedding at Sulaymaniyah University/College of Medicine's Animal House. They were provided with full access to food and water, placed in a 12-hour light/dark cycle, and the temperature was regulated at 22 ± 3°C. Prior to the experiment beginning, all rats experienced acclimatization for two weeks. The present study followed the standards for experimental animals and received approval from the College of Science's study ethics committee at Charmo University (Approval No. 10 on February 01, 2025; attached in the supplementary materials).

2.3 Experimental Design

The rats were randomly and equally divided into five groups, with five rats in each group. Group 1 (control group) received tap water via intragastric gavage as a placebo for five weeks. The rats in groups 2, 3, 4, and 5 were administered intraperitoneal injections (i.p) of 5-FU (20 mg/kg body weight) twice a week for 5 weeks. In addition, the rats in groups 3, 4, and 5 were concurrently administered curcumin daily via intragastric gavage (150, 300, and 450 mg/kg body weight, respectively) for five weeks (Table 1). Curcumin was dissolved in corn oil.

Table 1: Experimental groups and study design.

Groups	Dosage and administration route	No. of rats
Control	Water (i.g)	5
5-FU	20 mg/kg 5-FU (i.p)	5
Curcumin150 + 5-FU	150 mg/kg CUR (i.g) + 20 mg/kg 5-FU (i.p)	5
Curcumin300 + 5-FU	300 mg/kg CUR (i.g) + 20 mg/kg 5-FU (i.p)	5
Curcumin450 + 5-FU	450 mg/kg CUR (i.g) + 20 mg/kg 5-FU (i.p)	5

i.g: intragastric gavage route; i.p: intraperitoneal administration

2.4 Blood Sample Collection and Laboratory Analysis

On day 36, rats were weighed and euthanized by chloroform inhalation of 25% chloroform-soaked cotton in a sealed container, inducing unconsciousness within 2–5 minutes followed by death, in accordance with ethical guidelines. Immediately after euthanasia, the rats were dissected, and blood was carefully collected from the caudal vena cava and transferred into serum separator tubes. The serum was acquired when the blood was centrifuged at 4000 rpm for 10 minutes, using a Hettich centrifuge (Germany). The clear serum was tested to measure the level of alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (ALB), C-reactive protein (CRP), creatinine (SCr), and blood urea nitrogen (BUN) utilizing an automatic analyzer (Cobas pure c 303) with Roche Integra kits based on the manufacturer's instructions.

Furthermore, second blood samples were placed in EDTA tubes to measure the complete blood count (CBC) parameters, including white blood cells (WBC), red blood cells (RBC), platelets (PLT), and hemoglobin (HGB), to evaluate differences in these hematological parameters among the study groups using an automated hematology analyzer (Swelab alfa, Boule Diagnostics, Sweden).

2.5 Histopathological study

Histological preparation was initiated at the end of the trial. About 10 hours before sacrificing, the rats were subjected to fasting and then humanely euthanized. The liver and kidney organs were collected and weighed using a calibrated balance to determine their absolute weights. Thereafter, the organs were cut and placed into tissue cassettes and in a 10% neutral buffered formaldehyde solution for the fixation step for forty-eight hours. Following all histological processing steps, the tissue sections were stained with eosin and hematoxylin solution. The sections were analyzed under a bright-field light microscope.

2.6 Semi-quantitative lesion scoring

Generally, lesion scoring was estimated semi-quantitatively via image analyzer software

(AmScope, 3.7) using a microscope eyepiece camera (MD500, 2019), and tissue samples were analyzed under the bright-field light microscope (NOVEL XSZ-N107T, China). Following histological preparation, for liver sections, vacuolar degeneration and inflammatory cells were estimated and measured in percentages of calculated cell numbers from 10 randomly selected fields, whereas vascular congestion was evaluated in µm of selected areas and statistically calculated as a mean percentage.

On the other hand, kidney sections were analyzed for the presence of acute cellular swelling, inflammatory cell infiltration, and blood vessel congestion. Moreover, vascular congestions were measured in areas of µm, whereas tubular epithelial cellular swelling and inflammatory cells were counted in randomly selected 10 fields under magnification of 100X.

The mean percentage of all calculated values was expressed as the following lesion scoring and grading scores (score 0-10% as no lesions, score 10-25% as mild, score 25-50% as moderate, score 50-75% as severe, and score 75-100% as critical lesions).

2.7 Statistical analysis

All values were presented as mean ± standard deviation (SD). Group differences were evaluated using one-way analysis of variance (ANOVA), followed by Tukey's test for further comparisons, with the help of GraphPad Prism software (V.10.4.1). P-values ≤ 0.05 were considered significant.

3. Results

3.1 Effect of 5-FU and Curcumin on Liver Biomarkers

The 5-FU group produced a significant increase in the level of serum alanine aminotransferase (ALT) when compared to the control group ($p = 0.0039$). Curcumin 300 + 5-FU significantly lowers the ALT level compared to the 5-FU group ($p = 0.0006$). The other treatment groups (CUR150+5-FU and CUR450+5-FU) did not show statistically significant differences ($p > 0.05$) compared to either the control or 5-FU groups (Fig. 1a).

The level of aspartate aminotransferase (AST) in the 5-FU group was significantly elevated compared to the control group ($p = 0.0254$), but when curcumin 300 was added to 5-FU, the serum AST levels dropped significantly compared to just 5-FU ($p = 0.0022$). The other treatment groups (CUR150+5-FU and CUR450+5-FU) did not show statistically significant differences ($p > 0.05$) compared to either the control or 5-FU groups (Fig. 1b).

Alkaline phosphatase (ALP) levels were significantly elevated in 5-FU-treated rats compared to the control group ($p = 0.0281$). However, in all groups that received both curcumin and 5-FU, ALP levels decreased with increasing curcumin doses, although these changes were not statistically significant ($p > 0.05$) relative to either the control or 5-FU groups (Fig. 1c).

Albumin (ALB) levels were significantly increased in the CUR150+5-FU group compared to the control ($p = 0.0118$) and 5-FU group ($p = 0.0154$). However, the CUR300+5-FU and CUR450+5-FU groups showed no significant changes in serum ALB levels ($p > 0.05$) (Fig. 1d).

3.2 Effect of 5-FU and curcumin on renal biomarkers

Serum creatinine (SCr) levels showed no significant differences among the experimental groups in comparison with the control and 5-FU groups ($p > 0.05$) (Fig. 2a).

The 5-FU group exhibited a significant increase in Blood Urea Nitrogen (BUN) levels compared to the control ($p = 0.0391$). Conversely, all rats administered curcumin+5-FU showed reduced BUN levels; particularly, the CUR 450+5-FU group showed a significant decrease in BUN compared to the 5-FU group ($p = 0.0411$), while the other treatment groups showed no significant changes ($p > 0.05$) (Fig. 2b).

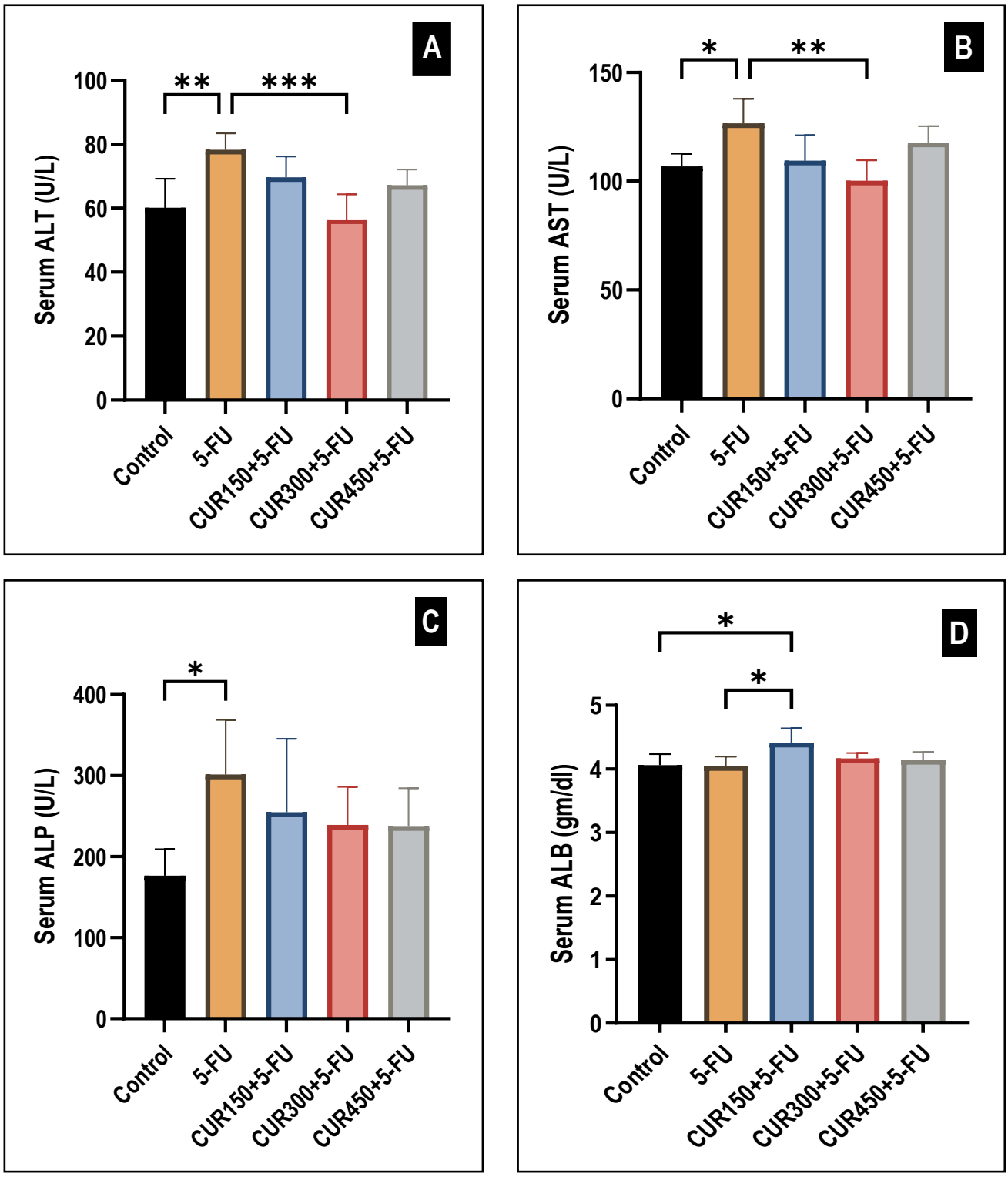

Figure 1: Effect of 5-FU and curcumin on serum levels of (A) ALT, (B) AST, (C) ALP, and (D) ALB. Data are expressed as mean ± SD. *p < 0.05, **p < 0.01, and ***p < 0.001 indicate statistically significant differences between groups.

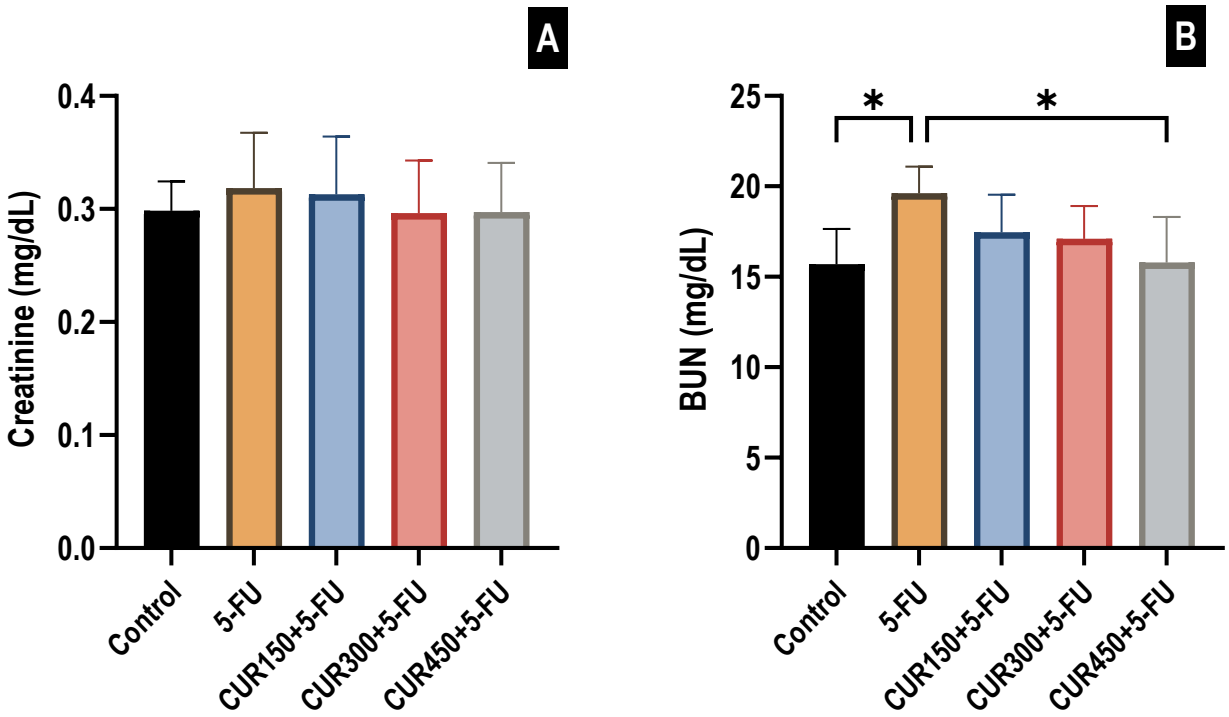

Figure 2: Effect of 5-FU and curcumin on (A) Creatinine, and (B) BUN levels Data are expressed as mean ± SD. *p < 0.05, **p < 0.01, and ***p < 0.001 indicate statistically significant differences between groups.

3.3 Effect of 5-FU and curcumin on plasma CRP levels

The C-reactive protein (CRP) levels decreased significantly in the groups treated with 5-fluorouracil combined with curcumin at doses of 450 and 300 mg/kg (p = 0.0367 and 0.0069, respectively) compared to the 5-FU group. Although a decrease in CRP levels was also observed in the CUR150+5-FU group, it was not statistically significant (p > 0.05) (Fig. 3).

3.4 Effect of 5-FU and curcumin on blood cells and HGB

White blood cell counts in the 5-FU and CUR150 + 5-FU groups showed significant decreases in comparison with the control group (p = 0.0037 and 0.0347, respectively). Additionally, the CUR300 + 5-FU group showed a significant elevation relative to the 5-FU group (p = 0.0453). while the CUR450 + 5FU group showed an increase that was not statistically significant (P > 0.05) (Fig. 4a).

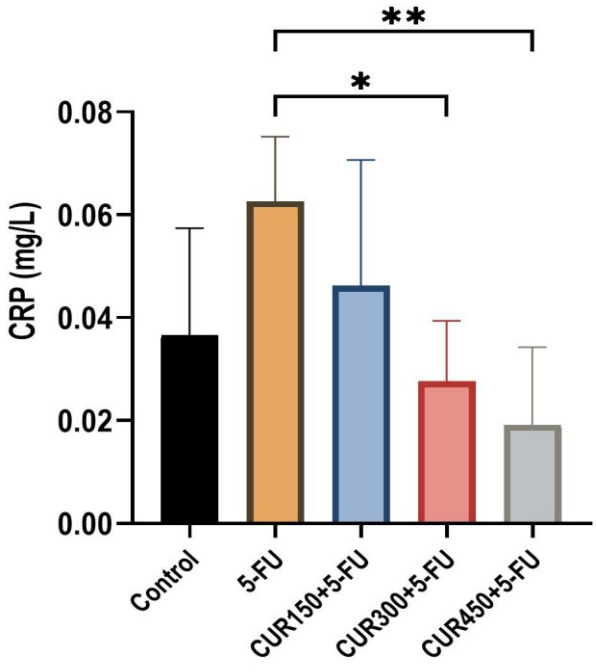

Figure 3: Effect of 5-FU and curcumin on CRP levels. Data are expressed as mean ± SD. *p < 0.05, **p < 0.01, and ***p < 0.001 indicate statistically significant differences between groups.

The red blood cell counts were significantly decreased in the 5-FU group compared to the control group (p-value = 0.0395). However, the CUR450 + 5-FU group showed a significant increase in RBC levels compared to the 5-FU group alone (p-value = 0.0322). No significant changes were observed in the CUR150 + 5-FU and CUR300 + 5-FU groups ($p > 0.05$) (Fig. 4b).

The platelet count in the CUR150+5-FU group showed significant elevation compared with the 5-FU group (p-value=0.027). Although the other groups treated with curcumin + 5-FU exhibited changes in PLT counts, these differences were not statistically significant ($P > 0.05$) (Fig. 4c).

Hemoglobin level in the 5-FU group showed a significant decrease compared to the control group (p-value = 0.0149). Other groups that received 5-FU along with curcumin (150 and 300) showed a statistically significant increase compared with the 5-FU group ($p = 0.0058$ and 0.0372, respectively). While the CUR450 + 5FU group showed not statistically significant ($P > 0.05$) (Fig. 4d).

3.5 Histopathological Findings of Liver

Hepatocellular morphological alteration and semiquantitative lesion scoring were illustrated in Fig. 5 and Table 2, respectively. Microscopical examination presents a severe to critical vacuolar degeneration, in addition to considerable engorgement of the central vein as well as significant infiltration of the inflammatory cells in liver sections isolated from animals injected intraperitoneally with 20 mg/kg of 5-FU twice a week (G2) in comparison to the normal histological architecture of liver in the control group (G1), with persistent normal morphological arrangement of hepatocytes around the central vein. In contrast to the 5-FU group, animals supplemented with curcumin as a hepatic toxicity preventive measure show significant lessening in the lesion severity outcome in a dose-dependent manner; hence, according to the semiquantitative table below, lesion grading has been reduced significantly from severe lesions in (G3) animals to moderate grade in (G4). Though, the results were much more significant in G4 and G5 as presented in the 300 and 450 mg/kg dosage protocols. In general, the lesion severity score has been significantly improved in the treated rats compared to the untreated 5-FU group.

3.6 Histopathological Findings of Kidney

As shown in Table 3, photomicrographs of kidney sections were evaluated in a semi-quantitative morphometric analysis, and the lesion scoring was analyzed statistically as a mean percentage. Remarkably, treatment with curcumin as a prophylactic measure to avoid renal damage with intraperitoneal injection (i.p) of 5-fluorouracil twice a week revealed significant $P < 0.05$ mitigation in the percentage of cellular swelling within the renal tubular epithelia as well as an overall lesion severity in terms of glomerular damage, infiltration of inflammatory cells and vascular engorgement from critical to severe and moderate lesion scores in a dose-dependent manner compared to animals in the model group (G2), which received i.p injection of 20 mg/kg 5-fluorouracil twice a week, which displayed critical and diffuse tubular degeneration and glomerular damage (Fig. 6). On the other hand, animals supplemented with curcumin show significant improvement in their lesion severity. Since lesion scoring has declined from severe in (G3) low doses of curcumin (150 mg/kg) to moderate lesion grades in both median and high-dose animals (G4 and G5) at 300 and 450 mg/kg, respectively. However, the alleviation in the morphometric measure was much more significant in the high-dose prophylactic regimen. Therefore, according to the morphological study, treatment with curcumin in the presented dosage schedule shows a significant reduction in lesion severity and overall improvement in the lesion scoring system, evidenced by a significant reduction in the number of degenerative cells and a decrease in the distribution of inflammatory cells.

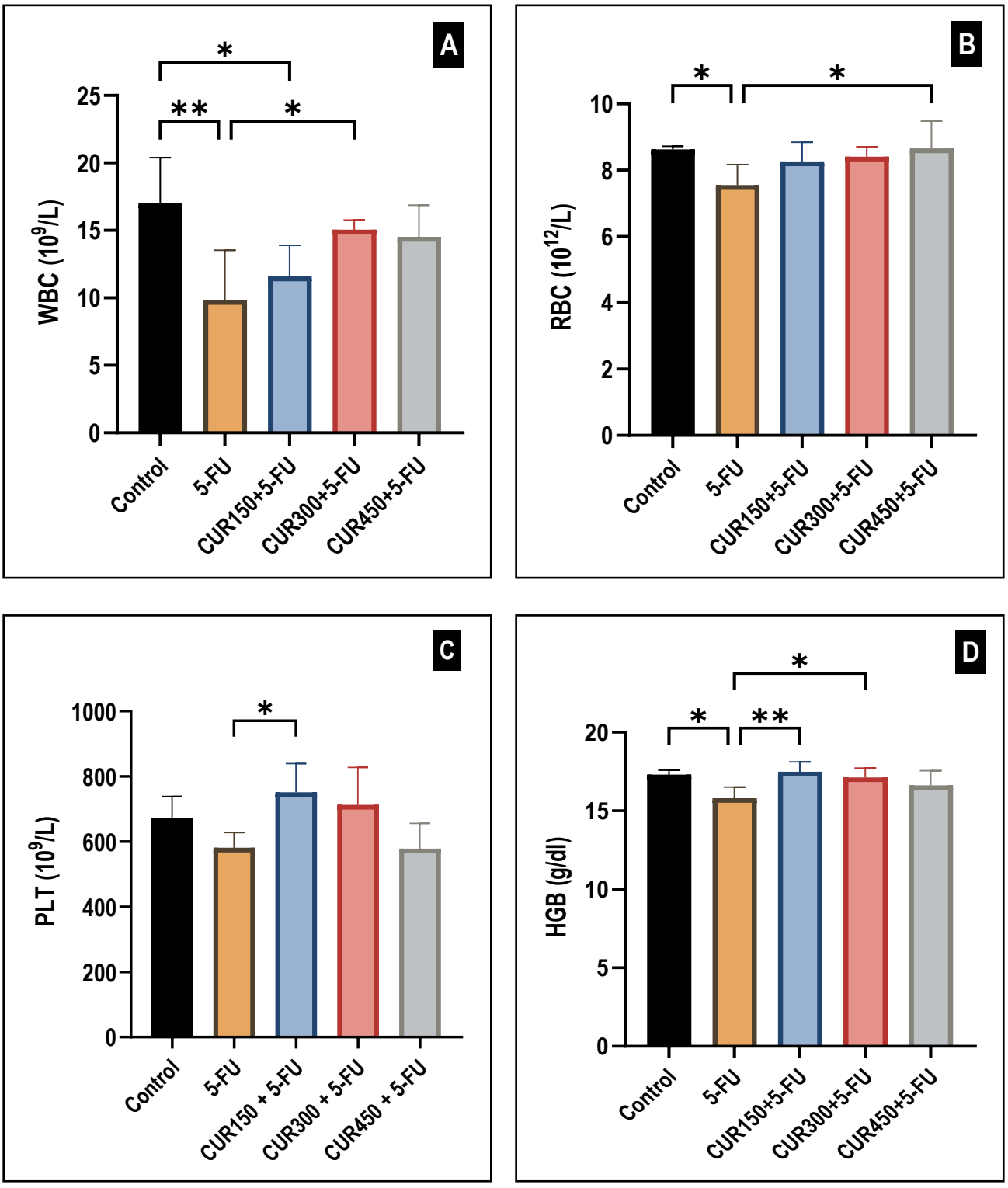

Figure 4: Effect of 5-FU and curcumin on (**A**) WBC, (**B**) RBC, (**C**) PLT, and (**D**) HGB**.** Data are expressed as mean ± SD. *p < 0.05, **p < 0.01, and ***p < 0.001 indicate statistically significant differences between groups.

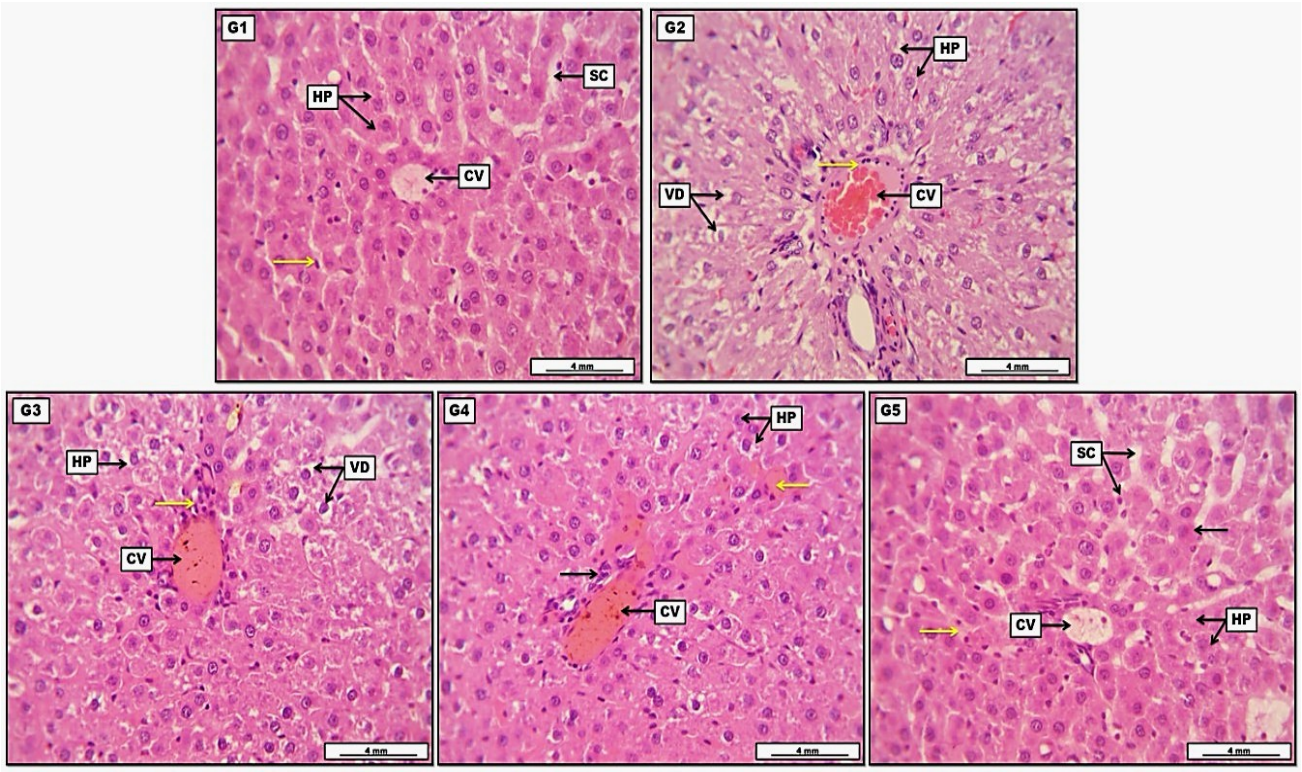

Figure 5: Photomicrographs of livers from **G1:** (control group) show no detectable structural alteration, designated by normally arranged radiated columns of hepatocytes (HP) around the central vein (CV) with characteristic sinusoidal capillaries (SC) enclosed with distributed Kupffer cells along their inner wall (yellow arrow). **G2** (5-FU) group demonstrates the presence of significant vascular congestion in the central vein (CV); moreover, the hepatocytes (HP) display severe and significant vacuolar degeneration within their cytoplasm. Additionally, the section also reveals leukocyte margination within the endothelial lining of the central vein (yellow arrow). **G3:** (CUR150+5-FU) group, elucidate the presence of severe and significant vacuolar degeneration (VD) within the radiated hepatocytes column (HP); furthermore, the section also shows significant vascular engorgement and congestion to the central vein (CV) with areas of perivascular infiltration of leukocytes (yellow arrow). **G4:** (CUR300+5-FU) group, demonstrates the presence of vascular congestion in the central vein (CV) together with some areas of perivascular cuffing (black arrow). The section expresses classically arranged hepatocytes (HP) with a low grade of cellular swelling. Moreover, the sinusoidal capillaries display low-grade dilation and engorgement with blood (yellow arrow). **G5:** (CUR450+5-FU) group, illustrate classically organized hepatocytes with slight cellular swelling (HP), together with normally appearing central veins (CV) and sinusoidal capillaries (SC) with no signs of vascular engorgement and congestion. Finally, the section reveals a moderate score of Kupffer cell hyperplasia (yellow arrow), with the presence of some deeply stained eosinophilic hepatocytes with hyperchromatic nuclei (black arrow). H&E. Scale bar: 4 mm.

Table 2: Semi quantitative evaluation of liver sections

Experimental Groups n=5	Vacuolar Degeneration* (Mean %) **	Vascular Congestion* (Mean %) **	Inflammatory Cells* (Mean %) **	Lesion Scoring (0 -100%)	Lesion Grading
(G1) Control	6.35 % A#	4,28 % A	9.72 % A	0-10 %	No lesion
(G2) (5-FU 20mg)	82.57% E	75.81 % E	76.49 % E	75-100 %	Critical
(G3) (5-FU+CUR 150mg)	72.46 % D	63.22 % D	56.73 % D	50-75 %	Severe
(G4) (5-FU+CUR 300mg)	36.78 % C	46.93 % C	32.89 % C	25-50 %	Moderate
(G5) (5-FU+CUR 450mg)	28.63 % C	33.71 % C	30.47 % C	25-50 %	Moderate

*Hepatocyte vacuolar degeneration and inflammatory cell infiltration were estimated in the mean (%) of cell numbers per calculated different selected field. Vascular congestion estimated in the area of a given section is calculated in µm. **Each number indicates the mean percentage (n=5). #Statistical comparison between groups: Mean values with different capital letters have significant differences at $P < 0.05$.

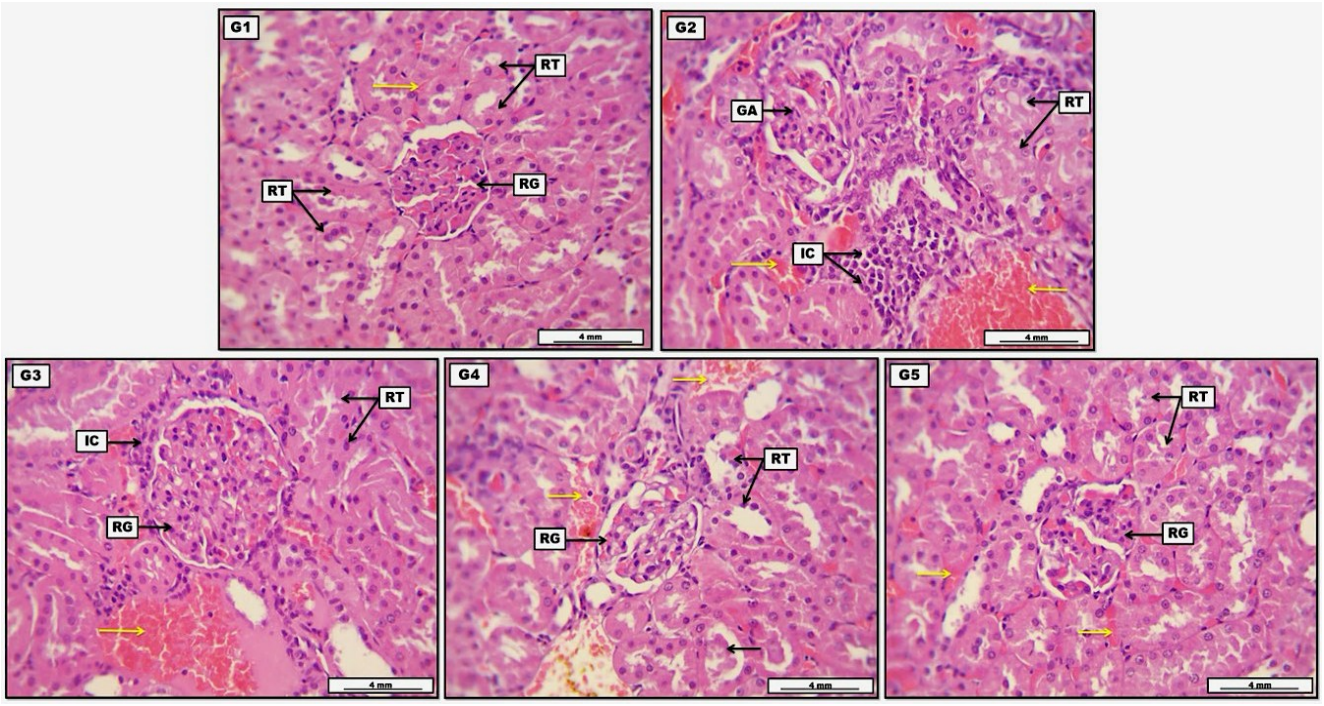

Figure 6: Kidney microscopy images from G1: the control group, shows the characteristic appearance of the renal glomerular structure (RG) with no obvious morphological changes. Renal tubules (RT) display no significant lesions, only low-grade cellular swelling with the presence of mild vascular congestion (yellow arrows) in the given section. G2: 5-FU group, showing severe and diffuse infiltration of inflammatory cells (IC), together with significant glomerular atrophy (GA). In addition to the presence of significant vacuolar degeneration within the renal tubular epithelium (RT). The section also reveals significant vascular engorgement and congestion (yellow arrows). G3: (CUR150+5-FU) group discloses the presence of significant vascular congestion (yellow arrow) within the renal vascular system, in addition to the pre-glomerular infiltration of inflammatory cells (IC). Moreover, the section also proves renal glomerular structure (RG), with the presence of cellular swelling with the renal tubular epithelia (RT). G4: (CUR300+5-FU) group, displays the presence of moderately scored vascular congestion and dilation (yellow arrows), with slightly atrophied renal glomeruli (RG). Other areas of the given section show a moderate degree of cellular swelling in the renal tubular epithelium (RT) with the presence of hyaline casts within their lumina (black arrow). G5: The (CUR450+5-FU) group reveals the presence of a moderate grade vascular congestion with the renal microcirculation (yellow arrows). Renal tubular epithelia (RT) show a low grade of cellular swelling, together with ordinarily appearing renal glomeruli (RG) with no apparent morphological lesions. H&E. Scale bar: 4 mm.

Table 3: Semi quantitative evaluation of kidney sections.

Experimental Groups n=5	Vascular Congestion* (Mean %) **	Cellular Swelling* (Mean %) **	Inflammatory Cells* (Mean %) **	Lesion Scoring (0 -100%)	Lesion Grading
(G1) Control	7.36 % ^{A}#	2.54 % ^{A}	8.64 % ^{A}	0-10 %	No lesion
(G2) (5-FU 20mg)	84.42 % ^{E}	78.91 % ^{E}	81.65 % ^{E}	75-100 %	Critical
(G3) (5-FU+CUR 150mg)	75.22 % ^{D}	66.75 % ^{D}	72.48 % ^{D}	50-75 %	Severe
(G4) (5-FU+CUR 300mg)	44.87 % ^{C}	36.81 % ^{C}	32.66 % ^{C}	25-50 %	Moderate
(G5) (5-FU+CUR 450mg)	36.94 % ^{C}	31.47 % ^{C}	27.38 % ^{C}	25-50 %	Moderate

*Renal tubular Cellular swelling and inflammatory cells were evaluated in (%) of the calculated mean percentage of cell numbers from different fields. Vascular congestion estimated in the area of a given section is calculated in µm. **Each value shows the mean percentage (n=5). #Statistical comparison between groups: Mean values with different capital letters have significant differences at $P < 0.05$.

4. Discussion

Hepatotoxicity and nephrotoxicity are among the main adverse effects associated with 5-FU (Sengul et al., 2021; Ali, 2012). The liver and kidneys, due to their central roles in metabolism, detoxification, and excretion, are particularly vulnerable to drug-induced toxicity and damage (Kalra et al., 2018; Ogobuiro and Tuma, 2023). Specifically, 5-FU toxicity has been linked to the generation of free radicals, resulting in lipid peroxidation, cellular membrane damage, and apoptosis (Gelen et al., 2021). In the present study, the protective effects of curcumin against 5-FU-induced liver and kidney toxicity in male Sprague Dawley rats were evaluated. The observed protective role of curcumin is likely attributed to its antioxidant, anti-inflammatory, and anti-apoptotic properties.

4.1 Biochemical and Histopathological Effects of Curcumin and 5-FU on the Liver

Liver enzyme levels such as alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), and albumin (ALB) protein are often used to assess liver damage. In our investigation, 5-FU significantly increased the levels of liver enzymes with marked histopathological damage in liver tissues. Our results were in agreement with the other investigations that found 5-FU raised the levels of liver enzymes (Gelen et al., 2017; Mahran et al., 2024; Fukuno et al., 2016; Pujari and Bandawane, 2021). Meanwhile, rats treated with curcumin, particularly at 300 mg/kg, significantly decreased the serum level of liver enzymes, especially ALT and AST, and protected normal liver tissues with its functions. These results support the hypothesis that curcumin shows protective efficacy in mitigating hepatic and renal damage. This finding corresponded with previous studies (Vajdi et al., 2025; Sun et al., 2020).

Liver injury results in membrane damage or necrosis, permitting intracellular enzymes to enter circulation and become detectable in serum (Gelen et al., 2017). The aminotransferases (ALT and AST) are the most frequently utilized and specific indicators of hepatocellular necrosis (Dama et al., 2011). In detecting drug-induced liver injury (DILI), ALT is a more specific marker compared to AST (Ozer et al., 2008). The increase in the levels of AST and ALT was probably due to the damage and loss of the functional integrity of liver cell membranes and endothelial linings caused by an increase of oxidative products and reactive oxygen species in liver tissue (Gelen et al., 2017; Sun et al., 2020). The elevation in AST and ALT occurs in more than 70% of patients treated with 5-FU (Sugarbaker et al., 1985). These results suggest that the hepatotoxic effects of 5-FU in rats may reflect similar pathophysiological mechanisms in humans, suggesting consistency across species.

Alkaline phosphatase (ALP) is another important liver enzyme, which is linked to membrane lipids in bile canaliculi ducts (Mahran et al., 2024). An increase in serum ALP levels, along with elevated ALT and AST

released from damaged hepatocytes due to membrane injury, indicates the presence of hepatocellular injury and suggests potential biliary dysfunction or impaired bile flow (Zhao et al., 2014). Curcumin similarly reduced the level of ALP; however, the reduction was not significant (Vajdi et al., 2025). While 5-FU elevated the level of ALP, this elevation was due to inhibition of bile excretion due to liver damage (Wright and Vandenberg, 2007).

In the current study, the level of ALB was approximately the same among both the control and the 5-FU group. However, curcumin (150 mg/kg) significantly raised the level of ALB in comparison with both the control and 5-FU groups. A lowered albumin level is generally linked to a reduction in albumin synthesis, commonly due to hepatotoxicity and chronic liver disease leading to hepatocyte apoptosis (Strang and Schunkert, 2014; Thapa and Walia, 2007, Elmansi et al. (2017) reported that the hepatoprotective effect of curcumin is mediated through multiple mechanisms, including the enhancement of hepatocyte viability via its antioxidant, antiapoptotic, autophagy-inducing, and antifibrotic properties, which may collectively contribute to the elevation of serum albumin levels and reduction of aminotransferases (Elmansi et al., 2017).

The liver histopathological results of this study indicate that the rat liver sections from the control group appear normal and healthy, showing no noticeable changes in structure. The tissue is characterized by the usual arrangement of radiating columns of hepatocytes around the central vein, with typical sinusoidal capillaries, scattered Kupffer cells along their inner wall, as illustrated in Fig.5, while in the 5-fluorouracil group, there is significant vascular congestion in the central vein, which indicates impaired hepatic circulation and suggests inflammation or liver injury. Moreover, the hepatocytes display severe and significant vacuolar degeneration within their cytoplasm due to high oxidative stress induced by 5-FU. Additionally, the section also reveals leukocyte margination within the endothelial lining of the central vein.

These modifications were significantly decreased in rats that received 5-FU along with curcumin, especially CUR300 and CUR450; lesion scoring also very significantly decreased from critical to severe to moderate in a dose-dependent manner, as shown in Table 2. Inflammation and oxidative stress are the major mechanisms related to liver toxicity, and curcumin reduces these effects due to its strong antioxidant, anti-inflammatory, antifibrotic, and hypolipidemic activity (Khan et al., 2019; de Porras et al., 2023).

Our findings strongly clarify the hepatoprotective effect of curcumin against 5-FU toxicity. Therefore, our results agree with prior studies (da Silva et al., 2023; Hashish and Elgaml, 2016; Kheiripour et al., 2021; Gelen et al., 2018).

4.2 Biochemical and Histopathological Effects of Curcumin and 5-FU on the Kidney

The kidney is a susceptible target organ of chemotherapy-induced toxicity. Nephrotoxicity is a severe adverse effect caused by chemotherapeutic drugs that lead to kidney injury by affecting function and damaging its structure (Zhou et al., 2011). The possible mechanism of 5-FU-induced renal toxicity is the induction of oxidative stress, activation of the apoptotic pathway through the upregulation of p53, Bax, and caspase-3, and the downregulation of Bcl-2, key proteins involved in inhibiting apoptosis (Duan et al., 2009). Curcumin has been shown to play a renoprotective effect in experimental kidney injury associated with chronic renal failure, ischemia and reperfusion, diabetic nephropathy, and nephrotoxicity, which is caused by various toxic agents and chemotherapies (Sun et al., 2020).

Serum creatinine (SCr) and blood urea nitrogen (BUN) are the most important indicators to reflect kidney injury levels and to identify the abnormal function of the kidney (Wang et al., 2018). The kidneys eliminate those substances, which are

common waste products of metabolism. BUN is a basic and indirect indicator that determines the condition of the liver and kidneys. BUN has a direct correlation with the kidney's excretory activity (Kamal, 2014). The elevation of BUN is frequently linked to renal insufficiency, while creatinine is normally used as an indicator of renal function and serves as the first step measurement for controlling the glomerular filtration rate (GFR) (Rosner and Bolton, 2006).

The present study demonstrated that 5-fluorouracil significantly increased blood urea nitrogen ($P<0.05$), while curcumin treatment led to a gradual decrease in BUN levels as its dosage increased. Particularly, a significant reduction was observed at CUR450 mg/kg, which effectively attenuated the 5-FU-induced elevation in serum BUN in rats. This renoprotective effect is likely attributable to curcumin's ability to reduce kidney damage, as supported by previous studies (Damiano et al., 2020; Najafi et al., 2015; Wu et al., 2017; Gelen et al., 2021).

The creatinine levels were lower in the rats that received both 5-FU and curcumin in comparison with the rats that received only 5-FU, but this difference was not statistically significant ($P > 0.05$). This result is consistent with previous reports by (Vlahović et al., 2007; Wu et al., 2020), where curcumin failed to demonstrate a protective effect on creatinine levels. One possible explanation is that SCr levels often remain unchanged until a significant loss of kidney function occurs, indicating that renal damage is either already present or happens before serum creatinine levels rise. SCr also doesn't accurately reflect kidney function right after acute changes in glomerular filtration rate until a steady-state equilibrium is reached, which may take several days (Nguyen and Devarajan, 2008).

The kidney histopathological results of this study indicated that the tissues of the control group were in a normal state, while the 5-FU caused severe and diffuse infiltration of inflammatory cells, significant glomerular atrophy, vacuolar degeneration, and vascular engorgement and congestion, as shown in Fig.6. It indicates the loss of a large number of functional glomeruli and the presence of 5-FU metabolites, including FBAL, which is an inactive metabolite that is frequently linked to renal dysfunction. These events caused renal function to decrease (Nishikawa et al., 2017; Baldelomar et al., 2018).

In the current study, administration of curcumin to rats significantly improved kidney tissue damage by reducing the inflammatory cells, cellular swelling within the renal tubular epithelia, lesion severity, degenerative cells, and congestion (Table 3), indicating that curcumin protects the kidneys by fighting inflammation, oxidation, and cell death caused by 5-FU. Consequently, our results agree with (da Silva et al., 2023; Wu et al., 2017; Damiano et al., 2020; Ali et al., 2022; Gelen et al., 2021).

4.3 Effect of curcumin and 5-FU on C-reactive protein

C-reactive protein (CRP) is an acute inflammatory protein made by liver cells that rises more than 1,000-fold in areas of inflammation or infection and is one of the most commonly used markers of overall inflammation in the body (Sproston and Ashworth, 2018). This study showed an elevation in serum CRP levels in rats that received only 5-FU (**0.0626±**0.0125) in comparison to those in the control group (0.0366**±**0.0207 mg/L). This elevation in CRP suggests a robust inflammatory response induced by 5-FU (Ali et al., 2022). In contrast, the administration of curcumin at dosages of 300 mg/kg and 450 mg/kg in combination with 5-FU resulted in a significant reduction in serum CRP levels to 0.0276 ± 0.0117 mg/L ($p = 0.0367$) and 0.0190 ± 0.0151 mg/L ($p = 0.0069$), respectively. The results indicate a dose-dependent anti-inflammatory effect of curcumin, effectively mitigating the 5-FU-induced systemic inflammation. Previous studies have also demonstrated that curcumin decreases CRP levels, which is in tune with our results (Mohammadi et al., 2017; Chandran and Goel, 2012).

This finding suggests that curcumin has a suppressive effect on NF-κB and the pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interferon gamma (INF-γ), interleukin-1 beta (IL-1β), IL-1, IL-2, IL-6, IL-8, and IL-12 (Goel et al., 2008; Reyes-Gordillo et al., 2007; Gukovsky et al., 2003). Furthermore, they support the hypothesis that the 5-FU-induced rat toxicity model involves activation of the inflammatory response system and can be ameliorated through anti-inflammatory interventions, as demonstrated in both in vitro and in vivo studies.

4.4 Effect of 5-FU and curcumin on blood cells and HGB

The hematopoietic system reflects the overall health status of the body, as it shows any changes in the animal's or human's body exposed to chemicals, toxic agents, and drugs (Yuan et al., 2014). 5-Fluorouracil is reported to have a hematotoxic effect (Anderson et al., 2012; Qian et al., 2015).

In this investigation, the 5-FU group showed a reduced number of circulatory cells and hemoglobin (HGB) compared to the control and the groups that received curcumin along with 5-FU. (Gelen and Şengül 2018) demonstrated The toxic effect of 5-FU on blood parameters induced a significant reduction in RBCs, and a decline in the values of HGB, WBCs, and hematocrit was recorded in 5-FU-treated rats as well. Therefore our results agree with (Safarpour et al., 2022; Gelen and Şengül, 2018), who observed that. 5-FU induces myelosuppression through the generation of oxidative stress in the bone marrow and damage to hematopoietic progenitors (Parchment et al., 1998; Numazawa et al., 2011), thereby impairing hematopoietic functions. Consequently, this may lead to a reduction in blood cell lifespan, resulting in decreased blood cell count and HGB levels. The continued daily use of curcumin largely affected and improved blood cell counts and hemoglobin levels. The observation in this study aligns with previous studies (Abubakar et al., 2020; Abd Allah et al., 2017; Abdel-Moneim et al., 2015) that clearly demonstrate that curcumin ameliorates hematotoxicity and could restore both RBC count and hemoglobin level effectively.

Curcumin-treated groups especially (CUR 300 mg/kg) showed a significant elevation in leukocytes when compared with the 5-FU group, which indicates that curcumin activates the animal's immune system (Çetin et al., 2010). The reduction in RBCs in rats treated with 5-FU may be due to different reasons, such as the breakdown of bone marrow cells or the enhancement of the osmotic fragility of RBCs. Thus, 5-FU poisoning represses the activity of hematopoietic tissues, disrupts erythropoiesis, and may lead to accelerated RBC breakdown anemia due to altered RBC membrane permeability, increased RBC mechanical brittleness, and impaired Fe metabolism (Gelen and Şengül, 2018). Another study demonstrated similar effects, showing that 5-FU induced changes in RBC rigidity, morphology, and ion balance, most likely by altering ATP levels in the RBC (Spasojević et al., 2005).

Concerning the platelet count, a notable elevation in curcumin-treated groups in combination with 5-FU, especially CUR 150 mg/kg, when compared with 5-FU alone, this finding is consistent with other studies. (Mortazavi Farsani et al. , 2020) reported that nanocurcumin is more effective in preventing chemotherapy-induced thrombocytopenia in mice by preserving bone marrow integrity and increasing the number of circulating platelets. Another study by the same authors in 2023 showed that the NF-κB pathway modulates several different genes, including those involved in apoptosis and immune responses, which help promote megakaryopoiesis (Mortazavi Farsani et al., 2023). Studies also reveal that curcumin can increase the platelet count and inhibit both the activation and aggregation of platelets (Hussain et al., 2022). One study also reported that profenofos-induced reduction in platelet count was attenuated by administration of curcumin (120 mg/kg) to mice for 30 days (Singh and Roy, 2014).

5. Conclusion

In conclusion, the biochemical, hematological, and histopathological findings of this study collectively indicate that curcumin exerts protective effects against 5-fluorouracil (5-FU)-induced hepatotoxicity, nephrotoxicity, and hematotoxicity in male Sprague-Dawley rats. Curcumin significantly reduced inflammation and key biomarkers of liver and kidney toxicity, while also improving select hematological parameters. Histological evaluations further revealed decreased inflammatory cell infiltration, lower lesion scores, and reduced tissue degeneration. Overall, the findings suggest that curcumin may serve as a promising adjunctive therapy to alleviate 5-FU-induced organ toxicity in cancer patients.

Conflict of interest.

The authors declare no conflict of interest.

CRediT authorship contribution statement.

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